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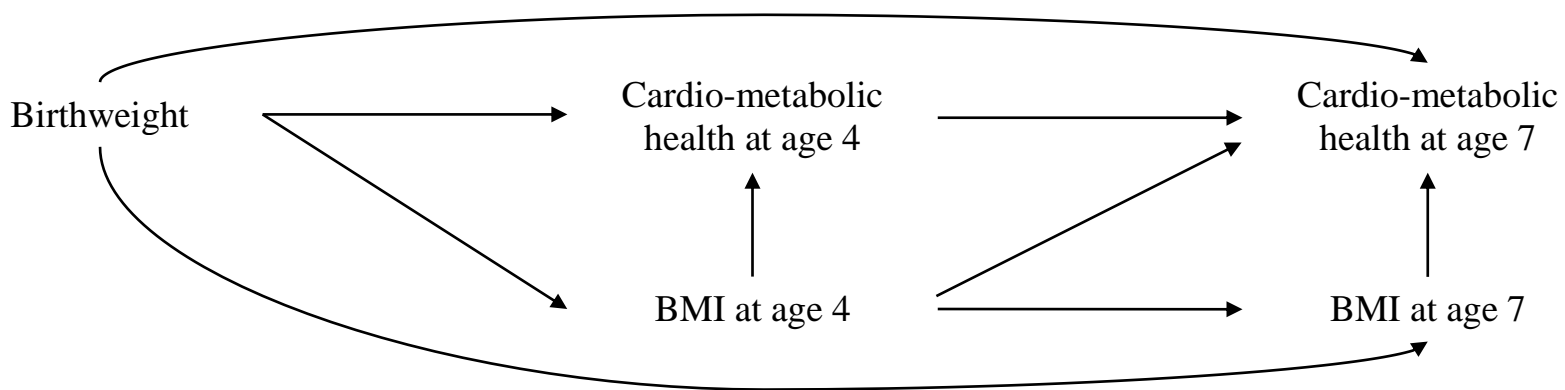
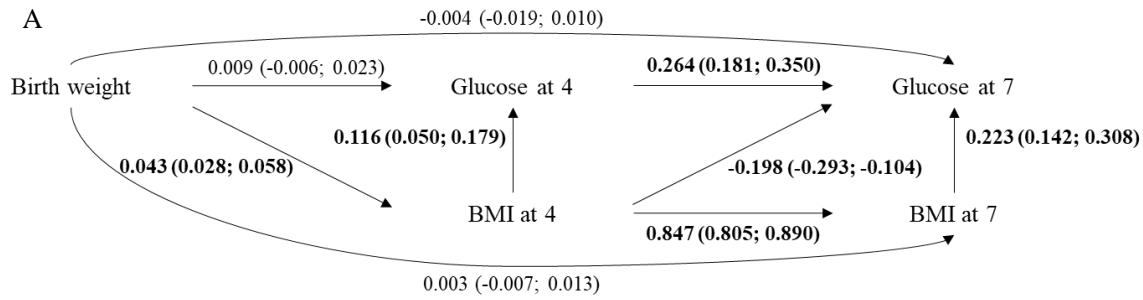
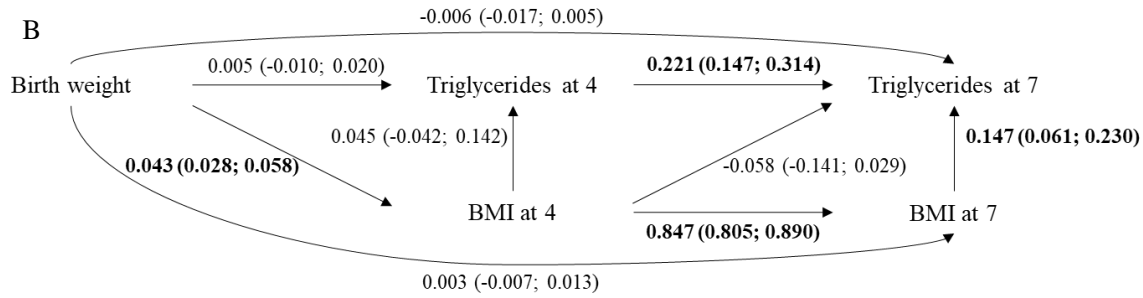


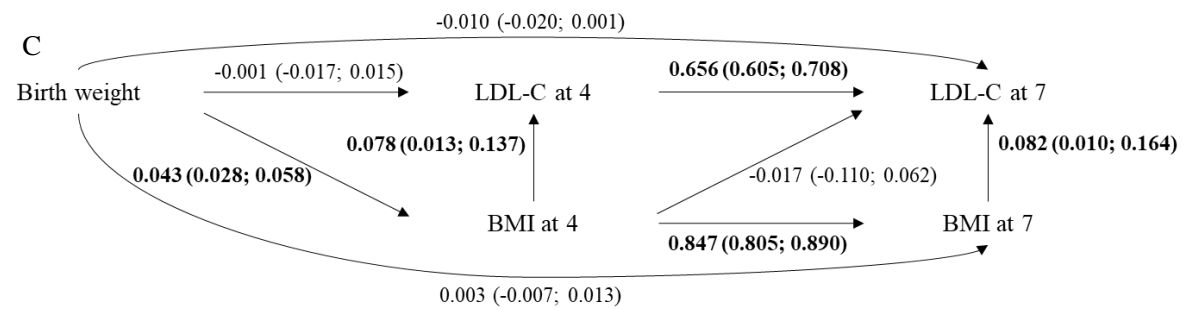
Fig. 1 Hypothesized mechanism linking birthweight with cardio-metabolic health at ages 4 and 7: an overall effect with direct and indirect (BMI-mediated) paths.



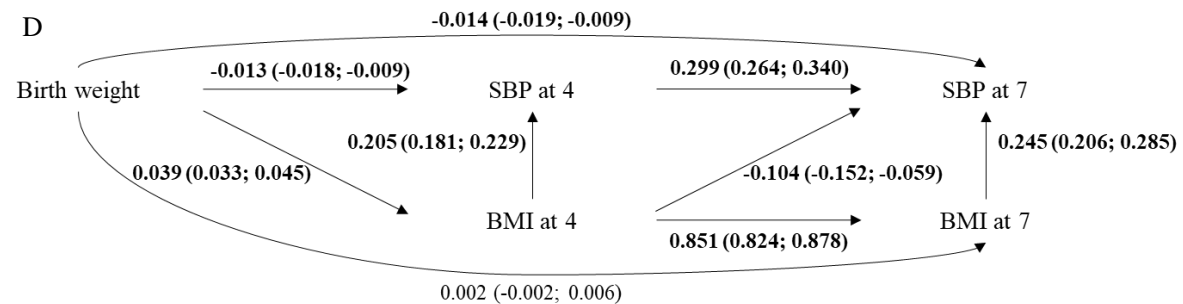
Model Chisquare = 2.956 Df = 4 Pr(>Chisq) = 0.565 RMSEA index = 0.000 90% CI: (0.000, 0.046) Bentler CFI = 1.000



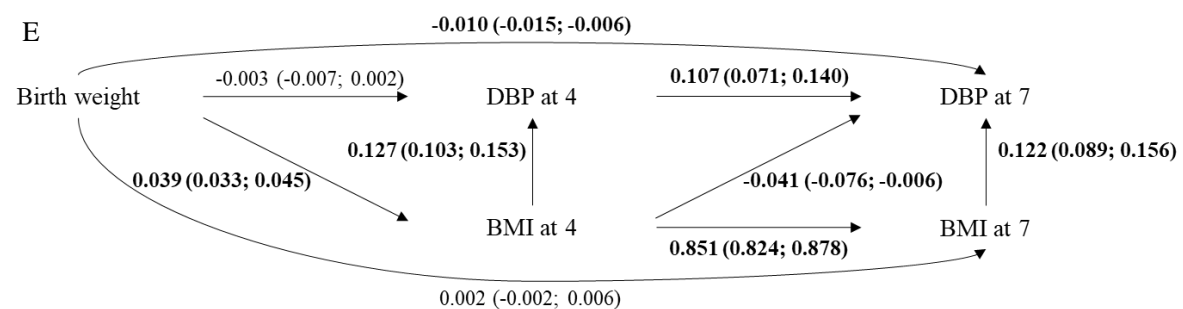
Model Chisquare = 5.767 Df = 4 Pr(>Chisq) = 0.217 RMSEA index = 0.023 90% CI: (0.000, 0.061) Bentler CFI = 0.998



Model Chisquare = 10.377 Df = 4 Pr(>Chisq) = 0.035 RMSEA index = 0.044 90% CI: (0.011, 0.077) Bentler CFI = 0.996



Model Chisquare = 22.674 Df = 4 Pr(>Chisq) < 0.001 RMSEA index = 0.038 90% CI: (0.024, 0.054) Bentler CFI = 0.996



Model Chisquare = 20.328 Df = 4 Pr(>Chisq) < 0.001 RMSEA index = 0.036 90% CI: (0.021, 0.052) Bentler CFI = 0.996

Fig. 2 Path analysis of the associations of birthweight with cardio-metabolic traits z-scores at ages 4 and 7 (A – Glucose; B – Triglycerides; C - LDL-cholesterol; D – Systolic blood pressure; E – Diastolic blood pressure)

Supplementary table 1. Comparison between eligible children included and not included regarding maternal, pregnancy, delivery and newborn characteristics.

	Not included n=3470	Included ^a n=4881	p
Maternal characteristics			
Education (years), mean (SD)	9.5 (4.0)	11.1 (4.3)	<0.001
Age at delivery (years), mean (SD)	27.8 (5.9)	29.8 (5.3)	<0.001
Pre-pregnancy BMI (kg/m ²), mean (SD)	23.8 (4.4)	23.90 (4.2)	0.363
Pregnancy and delivery characteristics			
Tobacco smoke during 3 rd trimester, n (%)	624 (18.3)	602 (12.5)	<0.001
Caesarean delivery, n (%)	1111 (32.6)	1788 (37.2)	<0.001
Newborn characteristics			
Gestational age (weeks), mean (SD)	38.6 (1.8)	38.7 (1.7)	0.118
Sex, n (%)			
Male	1779 (51.3)	2487 (51.0)	
Female	1691 (48.7)	2394 (49.0)	0.776
Birthweight (g), mean (SD)	3178 (509)	3191 (487)	0.223

Abbreviations: BMI, body mass index; SD, standard deviation.

^a Considered included if participant was included in the blood pressure analysis (n=4877) and/or in the glucose, LDL-cholesterol and triglycerides analysis (n=1031).

Supplementary table 2. Distribution of relevant characteristics by birth weight category.

	n	Birth Weight			p
		< 2500g	2500g - 4000g	≥ 4000g	
Body mass index (z-score), mean (SD)	4881				
4 years of age		0.21 (1.15)	0.62 (1.07)	1.00 (1.02)	<0.001
7 years of age		0.38 (1.28)	0.73 (1.18)	1.09 (1.14)	<0.001
Cardiometabolic traits (z-score), mean (SD)					
Glucose	1031				
4 years of age		-0.02 (1.24)	-0.04 (0.97)	0.36 (0.72)	0.070
7 years of age		-0.05 (1.24)	0.02 (0.94)	0.10 (0.98)	0.786
LDL-cholesterol	1031				
4 years of age		0.11 (1.11)	-0.03 (0.99)	-0.05 (1.04)	0.627
7 years of age		0.21 (0.97)	-0.07 (0.98)	-0.22 (0.81)	0.102
Triglycerides	1031				
4 years of age		0.00 (0.84)	0.00 (1.04)	-0.16 (0.83)	0.664
7 years of age		-0.02 (0.70)	-0.07 (0.90)	-0.19 (0.60)	0.682
Systolic blood pressure	4877				
4 years of age		0.42 (0.70)	0.42 (0.74)	0.25 (0.67)	0.025
7 years of age		0.79 (0.81)	0.69 (0.81)	0.59 (0.71)	0.023
Diastolic blood pressure	4877				
4 years of age		0.34 (0.71)	0.45 (0.70)	0.47 (0.69)	0.039
7 years of age		1.10 (0.69)	1.03 (0.68)	0.93 (0.62)	0.019
Maternal characteristics					
Education (years), mean (SD)	4855	10.7 (4.4)	11.1 (4.3)	10.9 (4.2)	0.219
Age at delivery (years), mean (SD)	4881	29.4 (5.5)	29.8 (5.3)	30.5 (4.8)	0.079
Pre-pregnancy BMI (kg/m ²), mean (SD)	4487	23.1 (4.0)	23.9 (4.2)	25.4 (5.0)	<0.001
Primipara, n (%)	4881	232 (69.5)	2565 (58.7)	79 (44.1)	<0.001
Pregnancy and delivery characteristics					
Gestational diabetes, n (%)	4854	28 (8.5)	269 (6.2)	18 (10.1)	0.036
Gestational hypertension, n (%)	4854	15 (4.5)	93 (2.1)	3 (1.7)	0.016
Pre-eclampsia / Eclampsia, n (%)	4854	33 (10.0)	30 (0.7)	0 (0.0)	<0.001

Tobacco smoke during 3 rd trimester	4814	58 (17.7)	534 (12.4)	10 (5.6)	<0.001
Gestational weight gain, mean (SD)	4569	11.5 (5.7)	13.6 (5.7)	15.5 (5.9)	<0.001
Caesarean delivery	4811	159 (48.8)	1527 (35.4)	102 (58.0)	<0.001
Newborn characteristics					
Gestational age (weeks), mean (SD)	4877	35.3 (3.0)	38.9 (1.2)	39.6 (1.0)	<0.001
Sex, n (%)	4881				
Male		164 (49.1)	2206 (50.5)	117 (65.4)	
Female		170 (50.9)	2162 (49.5)	62 (34.6)	<0.001

Table 1. Characteristics of the study sample at 4 and 7 years follow-up.

	n	4 years follow-up	7 years follow-up
Body mass index (kg/m ²), mean (SD)	4881	16.3 (1.8)	17.0 (2.5)
Glucose (mg/dL), mean (SD)	1031	78.7 (8.1)	83.2 (7.1)
LDL-cholesterol (mg/dL), mean (SD)	1031	103.2 (24.0)	98.9 (22.8)
Triglycerides (mg/dL), median (IQR)	1031	61.0 (30.0)	58.0 (32.0)
Systolic blood pressure (mmHg), mean (SD)	4877	98.1 (8.3)	105.0 (9.0)
Diastolic blood pressure (mmHg), mean (SD)	4877	57.7 (8.1)	69.7 (7.8)

1 Abbreviations: BMI, body mass index; SD, standard deviation.

1 Table 2. Unadjusted Pearson correlations coefficients of birthweight and BMI and cardio-metabolic traits z-scores in childhood.

	Birthweight	BMI 4y	Glucose 4y	TG 4y	LDL-C 4y	SBP 4y	DBP 4y	BMI 7y	Glucose 7y	TG 7y	LDL-C 7y	SBP 7y	DBP 7y
Birthweight	1	0.184**	0.057	0.012	0.003	-0.041*	0.053**	0.149**	0.003	0.001	-0.041	-0.062**	-0.072**
BMI 4y	-	1	0.128**	0.054	0.070*	0.293**	0.208**	0.801**	0.026	0.110**	0.089**	0.194**	0.107**
Glucose 4y	-	-	1	0.099**	-0.051	0.061*	0.046	0.098**	0.248**	-0.002	-0.008	0.024	0.017
TG 4y	-	-	-	1	0.018	0.031	0.043	0.003	-0.071*	0.235**	0.093**	0.019	0.036
LDL-C 4y	-	-	-	-	1	0.030	0.017	0.009	-0.027	0.052	0.667**	-0.010	0.039
SBP 4y	-	-	-	-	-	1	0.357**	0.249**	0.033	-0.001	0.009	0.310**	0.187**
DBP 4y	-	-	-	-	-	-	1	0.185**	0.027	-0.025	0.031	0.146**	0.143**
BMI 7y	-	-	-	-	-	-	-	1	0.114**	0.122**	0.062*	0.286**	0.167**
Glucose 7y	-	-	-	-	-	-	-	-	1	0.061	0.065*	0.120**	0.132**
TG 7y	-	-	-	-	-	-	-	-	-	1	0.023	0.074*	0.095**
LDL-C 7y	-	-	-	-	-	-	-	-	-	-	1	0.062*	-0.008
SBP 7y	-	-	-	-	-	-	-	-	-	-	-	1	0.541**
DBP 7y	-	-	-	-	-	-	-	-	-	-	-	-	1

Abbreviations: BMI, body mass index; birthweight, birthweight; DBP, diastolic blood pressure; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

*p<0.05

**p<0.01

Table 3. Estimated total, direct, and indirect (BMI-mediated) effect of birthweight (per 100g increase) on cardio-metabolic traits at 4 and 7 years of age.

	Total β (95% CI)	Direct β (95% CI)	Indirect (BMI-mediated) β (95% CI)
Model 1. Cardio-metabolic traits at age 4			
Glucose z-score	0.014 (-0.001; 0.029)	0.009 (-0.006; 0.023)	0.005 (0.002; 0.009)*
Triglycerides z-score	0.007 (-0.007; 0.020)	0.005 (-0.010; 0.020)	0.002 (-0.002; 0.006)
LDL-cholesterol z-score	0.002 (-0.015; 0.018)	-0.001 (-0.017; 0.015)	0.003 (0.001; 0.007)*
Systolic blood pressure z-score	-0.005 (-0.010; -0.001)*	-0.013 (-0.018; -0.009)*	0.008 (0.007; 0.010)*
Diastolic blood pressure z-score	0.002 (-0.002; 0.007)	-0.003 (-0.007; 0.002)	0.005 (0.004; 0.006)*
Model 2. Cardio-metabolic traits at age 7			
Glucose z-score	-0.001 (-0.014; 0.014)	-0.004 (-0.019; 0.010)	0.002 (-0.002; 0.005)
Triglycerides z-score	-0.001 (-0.013; 0.010)	-0.006 (-0.017; 0.005)	0.004 (0.001; 0.007)*
LDL-cholesterol z-score	-0.006 (-0.021; 0.008)	-0.010 (-0.020; 0.001)	0.005 (0.002; 0.008)*
Systolic blood pressure z-score	-0.011 (-0.017; -0.006)*	-0.014 (-0.019; -0.009)*	0.007 (0.005; 0.009)*
Diastolic blood pressure z-score	-0.008 (-0.012; -0.004)*	-0.010 (-0.015; -0.006)*	0.003 (0.002; 0.005)*

Abbreviations: LDL, low density lipoprotein; β , regression coefficient; CI, confidence interval.

Models adjusted for maternal pre-pregnancy BMI and tobacco smoke during 3rd pregnancy trimester.

*p<0.05